

LECTURE

Critical components for designing and implementing randomized controlled trials

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ABSTRACT

Randomized controlled trials (RCTs) are considered the first level of evidence to assess the efficacy of novel interventions/therapies. Proper design and implementation of an RCT can result in convincing causal inferences. RCTs often represent the gold standard for clinical trials when appropriately designed, conducted and reported. However, there are limitations in implementation of RCTs, including sufficiency of randomized allocation (especially for allocation concealment), implementing standard intervention, maintaining follow-up and statement of conflicting interests. Therefore, the basic principles of RCTs are outlined here so that pediatric investigators can further understand what is the best evidence based on RCTs. More importantly, the quality of pediatric RCTs may be improved by following challenges in pediatric clinical trials outlined here.

KEYWORDS

Randomized controlled trials, Design, Implementation, Consolidated Standards of Reporting Trials (CONSORT) statement

Introduction

Over the past three decades, thousands of randomized controlled trials (RCTs) have been conducted, some of which have provided new clinical treatment ideas resulting in changes to clinical practice. For example, systemic juvenile idiopathic arthritis (sJIA) does not always respond to available treatments, including anti-tumor necrosis factor agents. In 2008, Japanese researchers designed and conducted a randomized, double-blind, placebo-controlled, withdrawal phase III trial to investigate the efficacy and

safety of tocilizumab, an anti-interleukin-6-receptor monoclonal antibody, in 43 children aged 2–19 years that were diagnosed with sJIA.¹ The reported findings provided evidence toward confirming that tocilizumab treatment is suitable for controlling sJIA, which had been difficult to manage prior to this study. RCTs can also be used to fill a clinical gap in a specific disease field, for example, pediatric migraine. To find which medications could be used to prevent pediatric migraine headaches, Childhood and Adolescent Migraine Prevention (CHAMP) investigators conducted an RCT in which amitriptyline,

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topiramate and placebo were randomly allocated to children and adolescents aged 8–17 years that were experiencing migraine headaches.² After the 24-week treatment period, no significant difference in primary outcome (defined as a relative reduction of 50% or more in the number of headache days in the last 28 days of a 24-week trial compared with the 28-day baseline period) was observed between the groups. High quality multicenter RCTs can provide evidence to settle clinical controversy. For example, intensive insulin therapy for hyperglycemia in critically ill patients has become a standard in clinical practice, which was supported by several single center RCTs. In these single center RCTs, a statistically significant reduction of morbidity and mortality among adults in surgical intensive care units was shown in patients whose blood glucose levels were decreased to normal levels using insulin therapy.³ However, two meta-analyses based on these RCTs failed to show the same benefit.^{4,5} To confirm whether this clinical discrepancy exists in pediatric clinical practice, a multicenter RCT, called the Control of Hyperglycaemia in Pediatric Intensive Care (CHiP), was conducted in the UK. This trial showed that intensive glycemic control in critically ill children had no significant effect on the number of days alive and free from mechanical ventilation at 30 days after randomization.⁶ Therefore, high quality, well designed RCTs that are properly implemented and reported can promote the development of clinical medicine.

Why are RCTs regarded as the first level of evidence for intervention?

RCTs are considered the first level of evidence to assess the efficacy of novel interventions/therapies. The basic principle for designing and implementing RCTs allow for trial results that can demonstrate convincing causal inferences.⁷ The inherent advantages in RCTs that allow for strong causal inferences include a parallel controlled group, randomized allocation of study participants and blinding of study staff. Because of the principles outlined above, RCTs minimize potential bias and results in clinical evidence with a high level of validity. As described in Figure 1, potential bias can be minimized into several segments.

Criteria for selection of participants in RCTs must be both feasible and ethical so that sufficient volunteer participants can be recruited to adequately power the study for detection of effective differences among interventions, especially on the primary outcome. Careful determination of selection criteria for participants can increase the rate of primary outcome which would allow adequate power using a smaller sample size. It is also important that criteria for participants maximizes the generalizability of findings from the trial.

Obtaining informed consent from participants before random allocation can decrease the potential risk of

intervention rejection, which would result in a risk of bias from loss at follow-up. For consent to be ethically valid, it must be both voluntary and informed. Appropriate informed consent can minimize the possibility of coercion or undue influence from the study personnel. Undue influence is ethically problematic, particularly if it leads participants to discount the risks of a research project or seriously undermines their ability to decline to participate, eg. undue influence due to excessive payments to participants or enrolling students as research participants.

Randomization is one of the most important factors influencing the internal validity of clinical trials. Randomized assignment means that all subjects have the same probability of being assigned to different groups so that subjects are treated regardless of age, sex, or any other known or unknown prognostic baseline characteristics. Incomparable baseline characteristics can confound an observed association, especially those characteristics that are unknown or unmeasured. Randomization will result in equal distribution of non-research factors among different groups, and ensure comparability between groups at baseline to reduce the risk of selective bias.

Determining an appropriate control provides a reference to determine effectiveness of treatments tested in RCTs. The best control group receives no active treatment. As an example, a placebo, which is indistinguishable from active treatment, is generally required in clinical trials for newly developed drugs. This strategy compensates for any placebo effect of active intervention so that clear comparisons may be made to determine outcome differences between study groups that can be ascribed to a specific effect of the intervention. The intervention among different groups should be predefined and strictly carried out during RCTs. If not, post-randomization bias can occur due to incomparable interventions among different groups.⁸

Blinding is a strategy commonly used in RCTs, in which study participants, staff in contact with study participants, persons making measurements and those who determine study outcomes do not know study group assignments. Blinding is as important as randomization and is essential to improve the validity of outcome assessment and decrease both information and ascertainment bias.

Finally, a pre-designed statistical protocol will decrease the risk of selective reporting bias. Selective reporting bias arises from the following three types of reporting: selective reporting of only a partial set of pre-designed study outcomes rather than reporting all analyzed outcomes; selective reporting of specific outcomes at only select time points rather than reporting results from all time points tested; incomplete reporting of a specific outcome, for example, reporting the point estimate of risk ratio between treatments for an outcome but not giving a 95% confidence interval.⁹

TABLE 1 Advantages and disadvantages of alternative RCT* designs

Type	Advantages	Disadvantages
Factorial Designs ¹⁰	<ul style="list-style-type: none"> ◇ Increased research efficiency by answering two (or more) separate research questions in a single trial ◇ Appropriate design for studying effect modification (interaction) 	<ul style="list-style-type: none"> ◇ Increased complication of implementing ◇ Statistical analysis is more complex and results can be hard to interpret
Cluster RCTs ¹¹	<ul style="list-style-type: none"> ◇ Satisfies ethical requirements ◇ Helps avoid contamination between different interventions 	<ul style="list-style-type: none"> ◇ The statistical power is lower than in individual RCTs ◇ Sample size estimation and data analysis are more complicated
Adaptive Designs ¹²	<ul style="list-style-type: none"> ◇ RCTs can be changed based on interim analyses of the results to increase efficiency by altering the dose of study drug, the number of participants, or the duration of follow-up ◇ Allows earlier identification of the optimal dose and duration of treatment, ensures that a high proportion of participants receive the optimal treatment 	<ul style="list-style-type: none"> ◇ More complex to conduct and analyze ◇ Difficult to estimate cost and specific resources
Crossover Designs ¹³	<ul style="list-style-type: none"> ◇ Permits between-group, as well as within-group analyses ◇ Minimizes potential confounding because each participant serves as his own control ◇ Paired analysis increases the statistical power of the trial 	<ul style="list-style-type: none"> ◇ Doubles the duration of the study ◇ Adds to the expense as it is necessary to measure the outcome at the beginning and end of each crossover period ◇ Adds complexity of analysis and interpretation created by potential carryover effects
N-of-1 trails ¹⁴	<ul style="list-style-type: none"> ◇ Informs a single patient and clinical-care provider of the effects of a specific therapy for one patient ◇ Individual characteristics and genetic factors are eliminated as confounding variables ◇ Useful when the outcome variable responds rapidly and reversibly to the intervention ◇ Suitable for the effective assessment of rare diseases 	<ul style="list-style-type: none"> ◇ Generalizability of the results is limited ◇ Apparent efficacy of the intervention might be due to learning effects, regression to the mean, or secular trends ◇ More costly and time-consuming due to a greater number of periods during which different interventions are pursued

* RCT: Randomized controlled trials

Alternative RCT design

Classic RCT design with two parallel intervention groups may be not suitable for all clinical problems. There are a number of variations on the classic parallel group randomized trial that may be useful under certain circumstances. Table 1 shows several alternative RCT designs.

How to conduct a high quality RCT

RCTs represent the gold standard for clinical trials when appropriately designed, conducted, and reported.

At the study design stage, investigators should consider how participants will be allocated to each intervention group, and whether blinding is feasible. Another consideration is how well the intervention can be incorporated into clinical practice. The risk/benefit ratio of an intervention is uncertain until the efficacy of intervention can be proven by high quality RCTs. This uncertainty, termed equipoise, means that an evidence-based choice of interventions is not possible for participants of RCTs and therefore justifies random assignment. Another important part of a high quality RCT is to give standard intervention to all participants through the trial. The primary endpoint of the study should be predefined when designing the study protocol. Considering sample size, research duration and problems posed by multiple hypothesis tests, it is best to identify a single primary outcome. When composite end points are selected,

it should be noted that endpoint components should share a common pathophysiological basis. Composite outcomes usually provide more statistical power than a single outcome because more events can take place.¹⁵ However, misleading findings can occur when composite outcomes include events that are either not clinically relevant or more likely to occur relative to other outcomes.

At the implementation stage, it is important to consider the two most important features of randomization, which are generation of an unpredictable randomized allocation sequence and implementation of this sequence. The randomized allocation sequence should be concealed at least until patients have been assigned to their groups, this is termed allocation concealment. It should be noted that the persons responsible for sequence generation and sequence implementation should be different, otherwise, bias will be introduced. Clear comparison with standardized interventions for different groups should be strictly implemented; attention should be paid to changes in intervention that may introduce post-randomization bias.⁸ If this occurs, the strategy for detecting post-randomization bias should be stated in study reports. RCT designers should consider how they will measure adherence to the intervention; approaches such as self-report, pill counts, serum or urinary metabolite levels, or automated pill cap with a remote monitoring sensor, which can record pill counts automatically when the container is open, may be used.¹⁶ Sufficient actions should be taken to maintain the best compliance and follow-up rates possible.

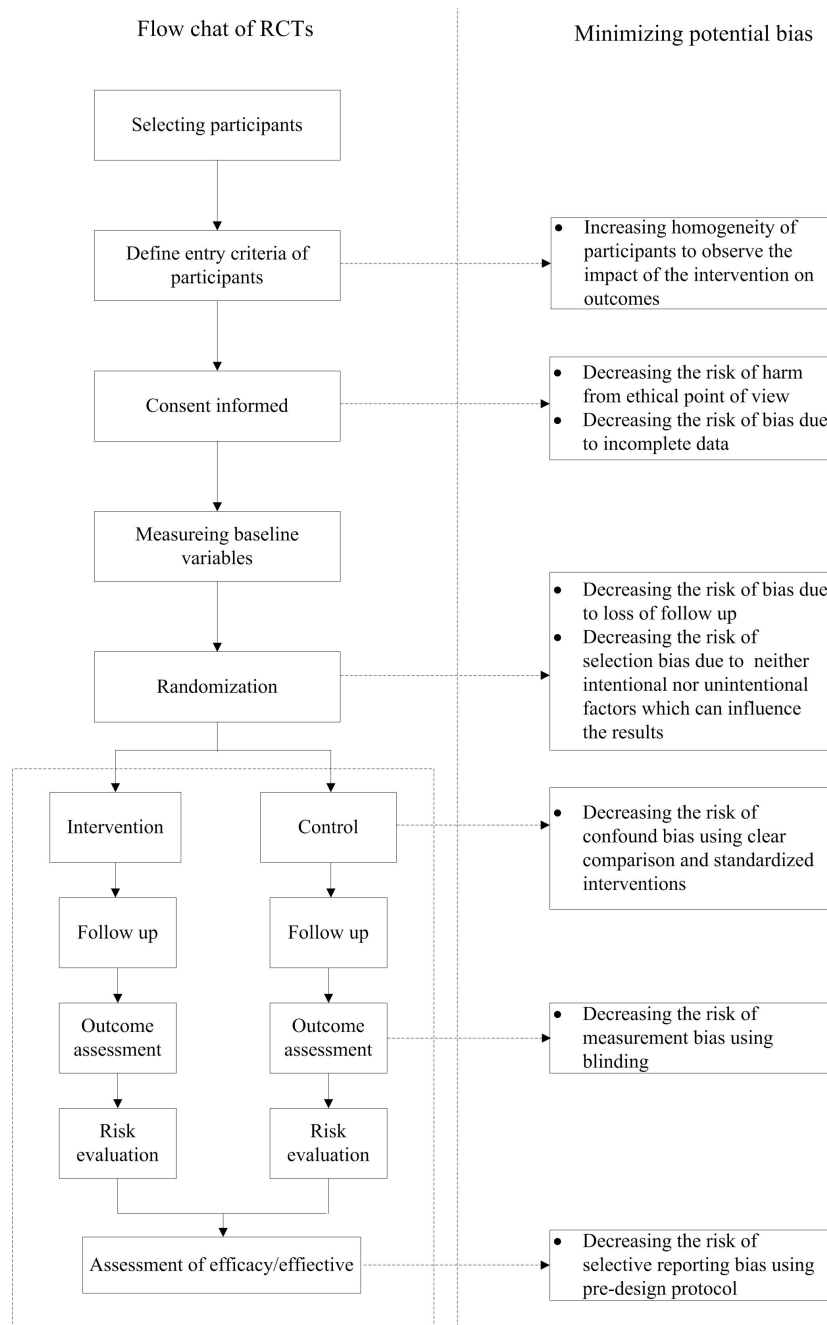


FIGURE 1 Flow chart demonstrating the principles of RCTs and how to prevent risk of bias for multiple stages of an RCT.

If participants violate the protocol or discontinue the trial intervention, they should be followed until the end of the RCT so that outcomes for these patients can be included in intention-to-treat analyses.

Challenges in pediatric clinical trials

Compared with adults, children’s clinical trials have their own particularities in ethical consideration, criteria for inclusion, selection and evaluation of outcome indexes. “Technical Guidelines for Clinical Trial of Drugs in Pediatrics” has been issued by Center for Drug Evaluation, CFDA (China Food and Drug

Administration) in 2016, in which the principles of “the minimal sample size, the least specimen and minimal pain” are recommended on the premise of meeting the requirements of evaluation.¹⁷ For example, strict regulations should be made on the operation methods and frequency of invasive testing so as to minimize repeated invasive detection steps. The potential risks, especially those that are not often considered in adult trials, such as fear, pain, separation from parents’ families, and effects of therapies on growth and development should be concerned and estimated critically. On the other hand, the age stratification of

pediatric population often is involved in drug clinical trials. The more comprehensive analysis on age stratification should be predesigned referring to the susceptible population of the target outcome, the pharmacological action characteristics and the safety of the intervention of clinical trials. In addition, the outcome indexes in pediatric clinical trials is also different from that in adults' clinical trials because children are in the physiological and psychological development, such as pain assessment, lung function examination, and some laboratory indexes. It is necessary to adopt appropriate assessment methods matching with target pediatric subjects' cognitive level. What's more, the follow-up period of pediatric clinical trial is usually longer than that of adult trial to observe the impact of interventions on growth and development. Therefore, the target organs or functions that may be affected, the time interval of follow-up, and methods for follow-up should be clearly defined in the protocol.

How to better report RCTs

At the reporting stage, it should be noted that insufficient reporting could both hinder readers from correctly evaluating the reliability and validity of the RCT findings and hinder researchers from extracting data for systematic reviews, which are regarded as the best source for evidence-based clinical practice. To help ensure accurate trial reporting, the Consolidated Standards of Reporting Trials (CONSORT) statement was developed¹⁸ and then updated in 2010.^{19,20} Taking into account the alternative conditions for RCTs, over 20 extended version of the CONSORT have been created and are posted on the EQUATOR collaboration network (<http://www.equator-network.org/reporting-guidelines/>) in conjunction with other CONSORT-related materials (<http://www.consort-statement.org>). Table 2 lists the CONSORT statement and extensions with their applicable research types.

TABLE 2 CONSORT statement and extensions with applicable research types

CONSORT statements and extensions	Applicable research type
Classic design	
<ul style="list-style-type: none"> CONSORT 2010 statement¹⁸ 	Classic RCTs
Specific designs	
<ul style="list-style-type: none"> CONSORT 2010 statement: Extension to cluster randomized trials¹¹ A literature review of applied adaptive design methodology within the field of oncology in randomized controlled trials and a proposed extension to the CONSORT guidelines¹² CONSORT extension for reporting N-of-1 trials (CENT) 2015 statement¹⁴ Improving the reporting of pragmatic trials: An extension of the CONSORT statement²⁰ Reporting guidelines for health care simulation research: Extension to the CONSORT and STROBE statements²¹ The stepped wedge cluster randomized trial: Rationale, design, analysis and reporting²² 	<ul style="list-style-type: none"> Cluster RCTs Adaptive RCTs N-of-1 trials Pragmatic RCTs Health care simulation research Stepped wedge cluster RCTs
Specific interventions	
<ul style="list-style-type: none"> CONSORT extension for Chinese herbal medicine formulas 2017: Recommendations, explanation, and elaboration²³ The CONSORT statement: Application within and adaptations for orthodontic trials²⁴ Reporting randomized controlled trials of herbal interventions: An elaborated CONSORT statement²⁵ Reporting of non-inferiority and equivalence randomized trials: Extension of the CONSORT 2010 statement²⁶ Revised standards for reporting interventions in clinical trials of acupuncture (STRICTA): Extending the CONSORT statement²⁷ CONSORT statement for randomized trials of non-pharmacologic treatments: A 2017 update and a CONSORT extension for non-pharmacologic trial abstracts²⁸ Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide²⁹ 	<ul style="list-style-type: none"> RCTs of Chinese herbal medicine formulas Within and adaptations for orthodontic trials RCTs of herbal interventions Non-inferiority and equivalence RCTs RCTs of acupuncture Abstracts of non-pharmacologic trials Description of interventions in publications
Specific outcomes	
<ul style="list-style-type: none"> Better reporting of harms in randomized trials: An extension of the CONSORT statement³⁰ Reporting of patient-reported outcomes in randomized trials: The CONSORT PRO extension³¹ CONSORT-Equity 2017 extension and elaboration for better reporting of health equity in randomized trials³² Checklist for the preparation and review of pain clinical trial publications: A pain-specific supplement to CONSORT³³ 	<ul style="list-style-type: none"> Harms-related data from RCTs Patient-reported outcomes in RCTs Health equity in RCTs Pain-specific RCTs
Specific application	
<ul style="list-style-type: none"> CONSORT 2010 statement: Extension to randomized pilot and feasibility trials³⁴ CONSORT for reporting randomized trials in journal and conference abstracts³⁵ 	<ul style="list-style-type: none"> Pilot and feasibility trials RCTs in journal and conference abstracts

Although the CONSORT statements have been developed for almost 20 years, implementation of these statements is not ideal. Researchers in the UK recently conducted a systematic review which included all RCTs concerning the outcomes of heart surgery in children and published in any language since January 2000. The aim of this review was to identify the current situation and reporting quality of the current literature surrounding this topic.³⁷ The results showed that most trials did not conform to the accepted standards of reporting, especially in the following areas: registration on a publicly accessible trial database, sample size calculation, participant flow chart and trial protocol publication. Similar results can be found in two other research reports focusing on RCTs in pediatric care,^{38,39} which reported that small and single-center studies with low value and uncertain quality provided limited evidence for clinical practice. For RCTs conducted in China, additional areas of weak compliance with reporting standards were identified, including conflict of interest statements, sufficient randomized allocation (especially for allocation concealment), maintaining standard intervention and methods of handling dropouts at both the implementation and statistical stages.⁴⁰

The basic principles of high quality RCTs are outlined here to help pediatric investigators further understand how to identify high quality RCTs that can provide the best evidence for application of novel therapies to clinical practice. It is important that the quality of pediatric RCTs be improved so that trial reports can provide physicians with better evidence to answer important questions relevant to pediatric clinical practice.

CONFLICT OF INTEREST

Xiaolu Nie, Yaguang Peng and Xiaoxia Peng confirm agreement with the final version of this manuscript and declare that there are no conflict of interest.

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